AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,358	02/05/2004	William Stern	P/546-279 REISSUE	8408

2352 7590 10/21/2005

OSTROLENK FABER GERB & SOFFEN
1180 AVENUE OF THE AMERICAS
NEW YORK, NY 100368403

EXAMINER	
HAGHIGHATIAN, MINA	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,358	STERN, WILLIAM	
	Examiner	Art Unit	
	Mina Haghighatian	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of Declaration, Remarks and IDS filed on 08/15/05. Accordingly claims 13-44 remain pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-14, 17, 20-23, 34 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Grebow et al (5,026,825).

Grebow et al teaches an intranasal formulations comprising calcitonin and excipients. The salmon and chicken calcitonins have a potency of about 4,000 to 6,000 MCR U/mg peptide (col. 3, lines 4-15). The said formulations may be administered across the nasal membranes as a spray, nose drop or aerosol (col. 11, lines 15-21).

Grebow also discloses that the nasal spray solutions are especially preferred with water or in a buffer at a **pH of between 3.0 and 8.0** using a buffer system including a mixture of sodium citrate and citric acid in the range of **0.01 M to 0.5 M**. This concentration was found effective to provide stability of the dissolved calcitonin in the diluent base or vehicle (col. 11, lines 35-47). Furthermore the formulations are said to have been made in 0.2M buffer at a pH value of 4.1; which meets the pH limitation of claims 13-14 stating a pH value of **about 3.9 or about 3.7** (col. 14, lines 34-35). The

preparations may also comprise other additives including stabilizers, tonicity adjusters, viscosity builders, preservatives and the like (col. 11, lines 48-52). The said additives include methyl paraben, propyl paraben, phenethyl alcohol, etc. Grebow discloses certain suitable concentration ranges of the said additives in the table of column 12.

Claims 13-14, 16-23, 34 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Kagatani et al (5,026,825).

Kagatani et al teach compositions for intranasal administration comprising calcitonin at least one absorption enhancer and liquid carriers and diluents suitable for application to the nasal mucosa (col. 1, lines 50-65). The clacitonins can be salmon calcitonin, human calcitonin, porcine calcitonin, etc (see paragraph bridging cols. 1 and 2). The agents used to enhance absorption of calcitonin include benzyl alcohol, Macrogol 400, ethanol, etc (col. 2, lines 3-13). The pernasal medical composition may be in the form of an aqueous solution. A buffer solution including citrates in a preferred **pH range of 3 to 5** is employed. The formulations also may contains polyoxyethylene sorbitan monooleate (col. 2, lines 16-49).

Kagatani also discloses that the aqueous solution for nasal administration comprises from 200 to 6000IU/ml of calcitonin (see col. 3, lines 5-10). Examples 1 and 4-6 show various ingredients such as salmon calcitonin, citric acid, sodium citrate, benzyl alcohol, etc, and their concentration ranges for the said formulations.

kagatani does not disclose a specific amount for surface active agents, it is considered that it would be at least 0.1%. Furthermore the examples of formulations indicate a **pH of 4.0**, which meets the limitation of **about 3.9 and 3.7** of claims 13-14.

Claims 13-14, 17, 20-23, 34 and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Veronesi et al (6,107,277).

Veronesi teaches formulations for intranasal administration comprising calcitonin, especially salmon calcitonin, citric acid and sodium citrate a buffers and other additives such as preservatives and surfactants. Various concentration ranges are disclosed for the said ingredients. The formulations preferably have a **pH value of from 3.6 to 4.5** (see col. 7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15, 24-28, 30-33, 35-39 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grebow et al (5,026,825) in view of Dua et al (The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits).

Grebow et al, discussed above, lacks disclosure on specific tonicity and viscosity of the intranasal formulations of calcitonin.

Dua et al compare the effect of different tonicity and viscosity levels of the formulation on absorption of the calcitonin from the nasal mucosa. Dua discloses studies performed with a formulation at a viscosity of about 1 and a formulation at a **viscosity of about 76 cp**. Dua also discloses that suitable tonicity for intranasal formulations of calcitonin is from **100 to 600 mOsm** and a **pH of about 4.0** was accomplished using buffers (see abstract and page 235, col. 1, lines 7-11). Dua concludes that the droplet size distribution produced by the metered nasal spray pump at 1 cps viscosity was gaussian and unimodal (see page 239, column 1, lines 45-47).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the intranasal formulations of calcitonin as disclosed by Grebow et al to include the viscosity and tonicity limitations of the intranasal formulations of calcitonin as disclosed by Dua et al with the reasonable expectations of successfully preparing efficient and stable formulations with suitable and recognized viscosity and tonicity for nasal administration.

Claims 14-15, 24-33, 35-39 and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kagatani et al (4,788,221) in view of Dua et al (The influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits).

Kagatani et al, discussed above, lacks disclosure on specific tonicity and viscosity of the intranasal formulations of calcitonin.

Dua et al compare the effect of different tonicity and viscosity levels of the formulation on absorption of the calcitonin from the nasal mucosa. Dua discloses studies performed with a formulation at a viscosity of about 1 and a formulation at a **viscosity of about 76 cp**. Dua also discloses that suitable tonicity for intranasal formulations of calcitonin is from **100 to 600 mOsm** and a **pH of about 4.0** was accomplished using buffers (see abstract and page 235, col. 1, lines 7-11). Dua concludes that the droplet size distribution produced by the metered nasal spray pump at 1 cps viscosity was gaussian and unimodal (see page 239, column 1, lines 45-47).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the intranasal formulations of calcitonin as disclosed by Kagatani et al to include the viscosity and tonicity limitations of the intranasal formulations of calcitonin as disclosed by Dua et al with the reasonable expectations of successfully preparing efficient and stable formulations with suitable and recognized viscosity and tonicity for nasal administration.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chiodini et al (5,719,122) teaches compositions comprising calcitonin in dosage forms including intranasal administration. The formulations comprise a mixture of citric acid and sodium citrate as buffers and other ingredients.

Response to Arguments

Applicant's arguments and the Declaration filed 08/15/05 have been fully considered but they are not persuasive.

Applicant argues that Grebow does not recommend a pH range within the claimed range. Applicant argues that example 6 has too much citrate and examples 7 and 10 provide for a pH outside of the claimed pH range. This is not persuasive because 1) Although the examples may contain a citrate level or a pH value that is not quite the same as those recited in the instant claims, the text of Grebow teaches that formulations may contain a citrate/citric acid in the range of 0.01M to 0.5M, and that the formulations may have a pH range of from 3.0 to 8.0 (see col. 11). 2) Instant claims recite a pH range of from ABOUT 3.5 to ABOUT 3.9. The term "ABOUT" is a relative term and there is no standard for ascertaining the requisite degree. Thus it is considered that a pH of 3.1 or 4.0 anticipates a pH of about 3.5-3.9. It is also noted that the independent claims of 13 and 15 employ a language that allows for the total amount of citric acid or citrate or their combination be unclear. The claims read "....concentration of a component selected from the group consisting of citric acid, citric acid salt AND a combination thereof...". Thus even if the total concentration range of the prior art is outside of the concentration range stated in the instant claims, it reads on the claims because the total concentration of the prior art includes a combination of the citric acid and citrate. However the instant claims can comprise up to 25 mM (claim 13) or 50 mM (claim 150) of **EITHER** citric acid **OR** citrate or a combination thereof. In other words it is impossible to determine the TOTAL amount of citric acid/citrate of claims 13

and 15. Therefore it is not possible to compare the instant invention with those of the prior art.

Applicant argues that Kagatani and Veronesi references also disclose formulations that fall outside the recited ranges of the instant claims. Here also the reasons cited above apply.

Applicant argues that Grebow and Veronesi do not teach the methods of using citric acid and/or citrate for improving stability or bioavailability. Applicant states that Grebow and Veronesi teach that citrates are used as buffers. This is not persuasive because stability and bioavailability are inherent properties of the formulations.

Applicant argues that Dua reference teaches away from instant invention because Dua teaches that isotonic formulations have a more enhanced bioavailability than hypertonic or hypotonic formulations. This is not persuasive because instant claims require an osmotic pressure of from ABOUT 250 to ABOUT 350 mOsm/liter. Dua teaches that isotonic formulations have enhanced bioavailability. Also fig. 5 on page 240 shows that osmolarity of about 200 has an acceptable bioavailability.

(It is noted that the original specification discloses a range of from about 260 to 380 mOsm and not 250-350mOsm).

Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L. Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mina Haghighatian
October 13, 2005

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER